Scientists find molecular trigger of schizophrenia-like behaviors and brain changes

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Authors of the new study from The Scripps Research Institute included Professor Jerold Chun (right), Associate Professor Beth Thomas and colleagues. Credit: Cindy Brauer, The Scripps Research Institute

Scientists at The Scripps Research Institute (TSRI) have identified a molecule in the brain that triggers schizophrenia-like behaviors, brain changes and global gene expression in an animal model. The research gives scientists new tools for someday preventing or treating psychiatric disorders such as schizophrenia, bipolar disorder and autism.

"This new model speaks to how schizophrenia could arise before birth and identifies possible novel drug targets," said Jerold Chun, a professor and member of the Dorris Neuroscience Center at TSRI who was senior author of the new study.

The findings were published April 7, 2014, in the journal *Translational Psychiatry*.

What Causes Schizophrenia?

According to the World Health Organization, more than 21 million people worldwide suffer from schizophrenia, a severe psychiatric disorder that can cause delusions and hallucinations and lead to increased risk of suicide.

Although psychiatric disorders have a genetic component, it is known that environmental factors also contribute to disease risk. There is an especially strong link between psychiatric disorders and complications during gestation or birth, such as prenatal bleeding, low oxygen or malnutrition of the mother during pregnancy.

In the new study, the researchers studied one particular known risk factor: bleeding in the brain, called fetal cerebral hemorrhage, which can occur in utero and in premature babies and can be detected via ultrasound.

In particular, the researchers wanted to examine the role of a lipid called

lysophosphatidic acid (LPA), which is produced during hemorrhaging. Previous studies had linked increased LPA signaling to alterations in architecture of the fetal brain and the initiation of hydrocephalus (an accumulation of brain fluid that distorts the brain). Both types of events can also increase the risk of psychiatric disorders.

"LPA may be the common factor," said Beth Thomas, an associate professor at TSRI and co-author of the new study.

Mouse Models Show Symptoms

To test this theory, the research team designed an experiment to see if increased LPA signaling led to schizophrenia-like symptoms in animal models.

Hope Mirendil, an alumna of the TSRI graduate program and first author of the new study, spearheaded the effort to develop the first-ever animal model of fetal cerebral hemorrhage. In a clever experimental paradigm, fetal mice received an injection of a non-reactive saline solution, blood serum (which naturally contains LPA in addition to other molecules) or pure LPA.

Ten weeks after the mice were born, they were tested for schizophrenia-like symptoms. The researchers found that female mice given LPA-containing serum or LPA alone displayed hyperactivity upon stimulation, showed anxiety and had increased numbers of dopamine-producing neurons—all which are characteristic of schizophrenia and other psychiatric disorders.

The real litmus test to show if these symptoms were specific to psychiatric disorders, according to Mirendil, was "prepulse inhibition test," which measures the "startle" response to loud noises. Most mice—and humans—startle when they hear a loud noise. However, if a

softer noise (known as a prepulse) is played before the loud tone, mice and humans are "primed" and startle less at the second, louder noise. Yet mice and humans with symptoms of schizophrenia startle just as much at loud noises even with a prepulse, perhaps because they lack the ability to filter sensory information.

Indeed, the female mice injected with serum or LPA alone startled regardless of whether a prepulse was placed before the loud tone.

Next, the researchers analyzed brain changes, revealing schizophrenia-like changes in neurotransmitter-expressing cells. Global gene expression studies found that the LPA-treated mice shared many similar molecular markers as those found in humans with schizophrenia. To further test the role of LPA, the researchers used a molecule to block only LPA signaling in the brain.

This treatment prevented schizophrenia-like symptoms.

Implications for Human Health

This research provides new insights, but also new questions, into the developmental origins of psychiatric disorders.

For example, the researchers only saw symptoms in female mice. Could schizophrenia be triggered by different factors in men and women as well?

"Hopefully this animal model can be further explored to tease out potential differences in the pathological triggers that lead to disease symptoms in males versus females," said Thomas.

More information: LPA signaling initiates schizophrenia-like brain and behavioral changes in a mouse model of prenatal brain hemorrhage,

Translational Psychiatry, 2015.